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The Ketogenic Diet and its Clinical Applications in Type I and II Diabetes

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INTRODUCTION

It has been shown that metabolic-based therapies, such as nutritional ketosis, are effective to contrast seizure disorders and various acute and chronic neurological disorders [1,2]. From a physiological perspective, glucose is the primary metabolic fuel for cells. However, many neurodegenerative disorders have been recently associated with impaired glucose transport and metabolism and with mitochondrial dysfunction causing energy deficits, such as in Alzheimer's disease, Parkinson's disease, general seizure disorders, and traumatic brain injury [3-7]. Ketone bodies and tricarboxylic acid cycle intermediates represent alternative fuels for the brain and can potentially bypass the rate-limiting steps associated with impaired neuronal glucose metabolism. Therefore, therapeutic ketosis (elevated blood ketone levels) can be considered as a metabolic therapy by providing alternative energy substrates, which may have potent cellular protective properties independent of their bioenergetic function [8]. It has been estimated that the brain derives over 60% of its total energy from ketones when glucose availability is limited [9]. In fact, after prolonged periods of fasting or ketogenic diet (KD), the body utilizes energy obtained from free fatty acids (FFAs) released from adipose tissue. Because the brain is unable to derive significant energy from FFAs, hepatic ketogenesis converts FFAs into ketone bodies—hydroxybutyrate (BHB) and acetoacetate (AcAc)— while a percentage of AcAc spontaneously decarboxylates to acetone. Large quantities of ketone bodies accumulate in the blood (up to 5 mM) through this mechanism. This represents a state of normal physiological ketosis and can be therapeutic. Ketone bodies are transported across the blood–brain barrier by monocarboxylic acid transporters to fuel brain function. Starvation or nutritional ketosis is an essential survival mechanism that ensures metabolic flexibility during prolonged fasting or lack of carbohydrate ingestion [1]. Therapeutic ketosis leads to metabolic adaptations that may improve brain metabolism, restore mitochondrial ATP production, decrease reactive oxygen species production, reduce inflammation, and increase neurotrophic factors' function [10]. It has been shown that KD mimics the effects of fasting and the lack of glucose/insulin signaling, which promotes a metabolic shift towards fatty acid utilization [11]. KD can only induce a modest blood ketone level elevation and requires extreme dietary carbohydrate restriction for maintaining sustained (therapeutic) levels of ketosis [9]. Prior to the advent of exogenous insulin for the treatment of diabetes mellitus (type II) in the 1920's, the general guidelines for therapy were represented only by dietary modifications. At the time, diet recommendations

aimed to control blood glucose (which in most cases was only glycosuria) and were dramatically different from current low-fat, high-carbohydrate dietary recommendations for patients with diabetes [12,13]. For example, Dr. Elliot Joslin's Diabetic Diet in 1923 consisted of "meats, poultry, game, fish, clear soups, gelatin, eggs, butter, olive oil, coffee, tea" and contained approximately 5% of energy from carbohydrates, 20% from protein, and 75% from fat [14]. A similar diet was advocated by Dr. Frederick Allen from the same period [15]. The aim of this review article is to analyze the current literature in matter of therapeutic ketosis and its successful clinical applications in diabetes type I and II, thus paving the road towards a wider and safer use of this metabolic approach in these patients.

Therapeutic ketosis approach in diabetes type I

Diabetic ketoacidosis is a life-threatening condition and a major cause of morbidity and mortality in children with type I diabetes. The deficiency of insulin leads to metabolic decompensation, causing hyperglycemia and ketosis that resolves with the administration of insulin and fluids. However, an induced state of ketosis is the basis for the success of the KD, which is an effective therapy for children with refractory epilepsy. Roxana and colleagues reported the case of a 2-year old girl who presented to the emergency department with 1-week history of decreased activity, polyuria, and decreased oral intake. Her past medical history was remarkable for epilepsy, for which she was started on the KD with a significant improvement. Her laboratory evaluation was compatible with diabetic ketoacidosis, and fluids and insulin were given until correction. Because of concerns regarding recurrence of her seizures, the KD was resumed along with the simultaneous use of insulin glargine and insulin aspart. Urine ketones were kept in the moderate range to keep the effect of ketosis on seizure control. Under this combined therapy, the patient remained seizure-free with no new episodes of diabetic ketoacidosis [16]. Diabetes type I seems to be more prevalent in epilepsy, and low-carbohydrate diets improve glycemic control in diabetes type II, but data on the use of the classic ketogenic diet (KD) in epilepsy and diabetes are scarce. Dressler and colleagues presented a 15-month follow-up of a 3 years and 6 months old girl with diabetes type I (on the KD), rightsided hemiparesis, and focal epilepsy due to a malformation of cortical development. Although epileptiform activity on electroencephalography (EEG) persisted (especially during sleep), clinically overt seizures have not been reported since the KD. An improved activity level and significant developmental achievements were noticed, glycosylated hemoglobin levels improved, and glycemic control was excellent, without severe side effects. This study demonstrated that diabetes does not preclude the use of the KD [17]. In 2006, a 4-year-old girl affected by pyruvate dehydrogenase deficiency, static encephalopathy, and seizure disorder was treated with KD and presented severe diabetic ketoacidosis. Pyruvate dehydrogenase deficiency is a rare genetic defect of mitochondrial energy metabolism that leads to inefficient glucose use and lactic acidosis. KD provides the brain with an alternate fuel source, but its implementation is in contrast with traditional diabetes management. Faced with this therapeutic dilemma, Henwood and colleagues maintained ketosis without compromising safety to optimize neurologic function and quality of life and simultaneously treated the child with KD and exogenous insulin. Moreover, a 28-month follow-up revealed excellent glycemic control, improved activity level, significant developmental achievements, and a catchup of linear growth from < 5th to the 50th percentile [18]. In 2014, Aylward and colleagues published an interesting case report on a successful treatment of a child affected by myoclonic astatic epilepsy and type I diabetes. The major challenge in these cases remains the distinction between diet-induced ketosis and diabetic ketoacidosis [19]. On another note, congenital hyperinsulinism (CHI) is the most frequent cause of hypoglycemia in children. In addition to increased peripheral glucose utilization, dysregulated insulin secretion induces profound hypoglycemia and neuroglycopenia by

inhibiting glycogenolysis, gluconeogenesis and lipolysis. As a consequence, the shortage of all cerebral energy substrates (glucose, lactate and ketones) might lead to severe neurological sequelae. Patients with CHI unresponsive to medical treatment can be subjected to near-total pancreatectomy with increased risk of secondary diabetes. In this context, the KD is intended to provide alternative cerebral substrates such ketone bodies. In 2015, Maiorana and his group treated a child with drug-resistant, long-standing CHI who suffered from epilepsy and showed neurodevelopmental abnormalities. After attempting various therapeutic regimes without success, near-total pancreatectomy was suggested to parents, who asked for other options. Therefore, Maiorana's group proposed KD in combination with insulin-suppressing drugs. The diet was continuously administered for 2 years. Soon after the first 6 months, the patient was free of epileptic crises, presented normalization of EEG, and showed a marked recover in psychological development and quality of life [20].

Very recently, another group studied whether very-low-carbohydrate high-fat diets could improve glycemic control without causing any ill health effects in adults with type I diabetes: 11 adults (7 men, 4 women followed a ketogenic diet (< 55 g carbohydrate per day) for a mean of 2.6 ± 3.3 years (β-hydroxybutyrate 1.6 ± 1.3 mmol/l), and then underwent sampling and analysis of fasting blood, and were fitted with a blinded continuous glucose monitoring for 7 days, in order to measure glycemic variability. Participants displayed no evidence of hepatic or renal dysfunction and an excellent glycosylated hemoglobin type A1C level profile with little glycemic variability [21].

Use of ketogenic diet in diabetes type II

The inability of current recommendations to control the epidemic of diabetes, the specific failure of the prevailing low-fat diets to improve obesity, cardiovascular risk, or general health and the persistent reports of some serious side effects of commonly prescribed diabetic medications, in combination with the continued success of low-carbohydrate diets in the treatment of diabetes and metabolic syndrome without significant side effects, underline the need for a revision of current dietary guidelines. The benefits of carbohydrate restriction in diabetes are immediate and well documented. At the same time, concerns about the efficacy and safety are conjectural rather than based on evidence. Dietary carbohydrate restriction reliably reduces high blood glucose, does not require weight loss (although is still best for weight loss), and leads to the reduction or elimination of medication. It has never shown side effects comparable to those seen in most drugs. Between 2003 and 2005, 4 studies have re-examined the effect of carbohydrate restriction on type II diabetes. The 1st study enrolled 54 diabetic patients (out of 132 total participants) and found that hemoglobin A1c improved to a greater degree over one year with a lowcarbohydrate diet compared with a low-fat, calorie-restricted diet [22,23]. The 2nd study enrolled 8 men with type II diabetes in a 5-week crossover feeding study that tested similar diets. Participants showed higher improvement in glycohemoglobin while on the low-carbohydrate diet than when on an eucaloric low-fat diet [24]. The 3rd study was an inpatient feeding study in 10 participants with type II diabetes. After only 14 days, hemoglobin A1c improved from 7.3% to 6.8% [25]. In the 4th study, 16 participants with type II diabetes who followed a 20% carbohydrate diet had improvement of hemoglobin A1c from 8.0% to 6.6% over 24 weeks [26]. This information is critical for patients on medication for diabetes who initiate a lowcarbohydrate diet because of the potential for adverse effects resulting from hypoglycemia. Later on, Feinman and colleagues presented a consistent evidence supporting the use of low-carbohydrate diets as the first approach to treating type II diabetes and as the most effective adjunct to pharmacology in type I [27]. The prevalence of type II diabetes is increasing worldwide, accounting for 85-95% of all diagnosed cases of diabetes. To date, clinical trials have provided evidence of benefits of low-carbohydrate ketogenic diets in terms of clinical

outcomes. However, the molecular events responsible for these improvements still remain unclear in spite of the high amount of knowledge on the primary mechanisms of both the diabetes and the metabolic state of ketosis. Molecular network analysis of conditions, diseases and treatments might provide new insights and help build a better understanding of clinical, metabolic and molecular relationships among physiological conditions. In 2010, Farrés and his group studied the relationship between a ketogenic diet and type II diabetes through systems biology approaches, and notably through creation and analyses of the cell networks representing the metabolic state in a very-low-carbohydrate low-fat ketogenic diet. They found a strong relationship between the insulin resistance pathway and the ketosis main pathway, providing a possible explanation for the improvement observed in previous clinical trials. Moreover, they hypothesized a direct implication of glucose transporters or inflammatory processes [28]. The safety and tolerability of very low-calorie-ketogenic (VLCK) diets are a current concern in the treatment of obese type II diabetes mellitus patients. Goday and colleagues recently evaluated the shortterm safety and tolerability of a VLCK diet (about 50 g of carbohydrate per day) in an interventional weight loss program including lifestyle and behavioral modification support (known as "Diaprokal Method") in subjects affected by diabetes type II. They found that a VLCK diet is more effective in reducing body weight and improvement of glycemic control than a standard hypocaloric diet with safety and good tolerance for patients [29]. Dietary treatment is important in management of type II diabetes or pre-diabetes, but uncertainty exists about the optimal diet. Saslow and colleagues conducted a study in which they randomized adults with glycated hemoglobin > 6.0% and elevated body weight (body mass index > 25) to a VLCK diet or a moderate-carbohydrate, calorie-restricted, low-fat (MCCR) diet. All participants were encouraged to be physically active, get sufficient sleep, and practice behavioral adherence strategies based on positive affect and mindful eating. In a 12-month trial, adults with elevated glycated hemoglobin and body weight assigned to an VLCK diet had greater reductions in glycated hemoglobin, lost more weight, and reduced more medications than those instructed to follow an MCCR diet [30]. Pharmacologic agents currently approved for use in children with type II diabetes (metformin and insulin) are less than optimal for some patients. Steven and his group evaluated the use of a VLCK through a chart review of a group of children and adolescents affected by diabetes type II. Variables (body mass index, blood pressure, glycated hemoglobin A1c, blood glucose, and treatment regimens) were examined before, during, and up to 2 years after the diet and compared with a control group. Sustained decreases in body mass index and insulin requirements were observed in patients remaining on the VLCK for at least 6 weeks when compared with those of the control group. Blood glucose control and body mass index significantly improved, allowing the discontinuation of exogenous insulin and other antidiabetic agents [31]. In addition, it was found that limiting both protein and carbohydrates as in a classic KD remarkably reduced blood glucose in animal models of type I and type II diabetes and reversed diabetic nephropathy. [32]. Recently, an interesting manuscript came to light, focused on the effect of KD in preventing the induction of diabetes using streptozotocin (STZ) in rats using biochemical and histological methods. Animals were divided into 3 groups: normal diet, KD, and high carbohydrate diet. Specific diets ad libitum were given to each group of animals for a period of 8 weeks. In addition, each group was further subdivided into normal control, sham control and diabetic groups. Animals in the diabetic group were given a single intraperitoneal injection of STZ (55 mg/kg). After STZ injection, blood glucose levels of all groups increased significantly except for the group fed on KD. Also, food intake, water intake and urine output were significantly increased in all groups except for the KD group. There was also a significant decrease in weight gain of the animals fed on a KD. Although substantial decrease in the number of β cells was noticed in diabetic rats, there were no change in the number of β cells in the KD

treated diabetic animals compared to the KD control group. Authors concluded that KD prevents the development of diabetes using STZ in rats [33]. Moreover, Westman and colleagues tested the hypothesis that a diet lower in carbohydrates would lead to greater improvement in glycemic control over a 24-week period in 84 patients with obesity and type II diabetes, following a strict ketogenic diet (<20 g of carbohydrate/day) or a low-glycemic, reduced-calorie diet (500 kcal/day deficit from weight maintenance diet). Dietary modifications led to improvements in glycemic control and medication reduction/elimination in motivated volunteers. Overall, the diet lower in carbohydrates led to greater improvements in glycemic control, and more frequent medication reduction/elimination than the low glycemic index diet [34]. In this perspective, Simeone's group highly contributed to the field by publishing a number of studies. Notably, they found that the transcription factor peroxisome proliferator-activated receptor γ (PPARγ) contributed to the KD mechanism of action. In fact, KD increases brain PPARγ and the consequent inhibition or genetic loss of PPARγ prevents the anti-seizure effects of the KD on acutely induced seizures in non-epileptic mice [35] and spontaneous recurrent seizures in epileptic mice [36]. In addition, they tested the hypothesis that adjuvant treatment of KD-treated mice with a PPARγ agonist, pioglitazone, would result in an additive effect and they demonstrated, through isobolographic analysis, a synergistic interaction between KD and pioglitazone. They concluded that a co-administration may lead to the reduction of KD ratio without loss of seizure protection [37]. Back in 1978, a study on the effects of diet-induced ketosis on the signs of hypoglycemia on mice was published. Lard, medium chain triglycerides, or 1,3-butylene glycol comprised 43% of the diet fed to mice. Notably, the diet containing lard or medium chain triglycerides greatly protected the animals from the manifestations of acute insulininduced hypoglycemia. Furthermore, both diets protected the animals from the effects of repeated insulin injections (every 8 hours) for 10 days. In contrast, 1,3-butylene glycol had no protective effects. These experiments suggested that KD may be pivotal in the treatment of recurrent hypoglycemic conditions [38]. Afterwards, in the late 90's, two commercial enteral formulas for diabetic patients were made available in Spain: a high complex-carbohydrate, low-fat formulation (HCF) and a low-carbohydrate formulation (RCF). In 1998, a study compared the effects of these two formulas in 52 patients affected by non–insulindependent diabetes type II treated with sulfonylurea or insulin. The glycemic response of patients to the HCF was significantly greater than to RCF, but lower than in the sulfonyl type II diabetes treated groups. In addition, glucose, insulin, and C-peptide responses were higher in HCF than RCF groups. Authors concluded that the partial replacement of complex digestible carbohydrates with monounsaturated fatty acids in the enteral formulas for supplementation of oral diet might improve glycemic control in patients with type II diabetes [39]. It is renown that obesity is closely linked to the incidence of type II diabetes. The effective management of body weight and changes to nutritional habits, especially concerning the carbohydrate content and glycemic index of the diet, have beneficial effects in obese subjects with glucose intolerance. In this perspective, Dashti and colleagues documented the beneficial effects on glucose control of a KD in 64 obese diabetic subjects for 56 weeks, and thus demonstrated its safety [40]. Later on, Hussain showed that a long-term KD favorably alters cardiac risk factors even in hyperlipidemic obese subjects. In addition, it can help to significantly reduce antidiabetic medication dosages. Overall this group demonstrated that there exist beneficial effects of a KD over the conventional low-carb diet in obese diabetic subjects, where KD improves the glycemic control [41,42]. In a recent study, named PURE, Ravichandran's group showed that in a pool of over 135,000 patients from 18 countries nutritive carbohydrates increase human mortality, whereas dietary fat reduces it, thus leading to the novel concept of requesting a fundamental change of current nutritional guidelines. Concurrently, experimental evidence from animal models provided synergizing mechanistic concepts and pharmacological options

to mimic low-carb or ketogenic diets [43]. Back in 2012, Okuda investigated whether the improvement in hyperglycemia by dietary control influenced hyperglycemia-induced pathologies in tissues of juvenile obese mice. He found out that hyperglycemia promoted hepatic steatosis via the liver lipogenic pathway, although the development of steatosis may be prevented by feeding mice with a KD. Okuda's group showed that steatosis was dependent on the composition of fatty acids in the total lipids of the liver and serum [44]. Moreover, another group investigated the effects of KD and ketones on insulin resistance and secretion in non-obese type II diabetic rats and their mechanism in pancreatectomized diabetic rats for 5 weeks. The authors found that KD impairs energy and glucose homeostasis by exacerbating insulin resistance and attenuating hypothalamic leptin signaling. However, these changes were not associated with increased serum ketone levels [45]. Taken together, these findings on animal and human models lead to the conclusion that the therapeutic ketosis approach should be considered as a valid metabolic alternative in the treatment of patients affected by diabetes type I and II. In addition, ketogenic diets at different ratios (according to specific clinical cases and pathology degree) should be taken into serious consideration as a possible standard therapy in the future treatment panorama of diabetes.

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